UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/420,692	10/19/1999	JEFFREY M. BESTERMAN	106.101.197	3139

32254 7590 10/22/2004

KEOWN & ASSOCIATES
500 WEST CUMMINGS PARK
SUITE 1200
WOBURN, MA 01801

EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/420,692	BESTERMAN ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 24 September 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *please see attached*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *None*.

   Claim(s) objected to: *None*.

   Claim(s) rejected: *1-3,6 and 13*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☒ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). *3-3-04*.

10. ☐ Other: _____

Attachment

The IDS filed 3-3-04 contains citations C3 and C4, which are European Search Reports. These search reports have been considered by the examiner, but are crossed out because they cannot be listed as references in a published patent since they are not citations to a particular reference.

Claims 1-3, 6 and 13 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting the expression of human DNA methyltransferase-1 in vitro and in vivo comprising the systemic administration of antisense MG88 and MG98, and being enabling for a method for inhibiting tumor growth in vitro and in vivo comprising the systemic administration of antisense MG88 and MG98, and enabling for the synergistic reduction in human non-small cell lung, human colon and human bladder tumor cell growth in vitro following administration of antisense (MG88 or MG98) and 5-aza-dC, for a synergistic increase in expression of $p24^{WAF1}$ and p16 proteins in human bladder tumor cells in vitro following administration of antisense (MG88 or MG98) and 5-aza-dC, and for a synergistic reduction in human colon and human bladder tumor cell growth in vivo following intravenous administration of antisense (MG88 or MG98) and 5-aza-dC, does not reasonably provide enablement for methods for inhibiting tumor growth or treating a disease comprising the administration of any antisense oligonucleotide that specifically targets human DNA methyltransferase-1, or synergistic treatment or effects comprising the administration of any antisense that specifically targets human DNA methyltransferase-1 and any protein effector of human DNA methyltransferase-1 for the

same reasons of record set forth in the Office actions mailed 2-13-04 and 8-24-04. In their request for reconsideration filed 9-24-04, , Applicants argue that the experiments required to enable the full scope of the claimed invention would not be undue, and would only require some screening using the method exemplified in Example 6. Example 6 teaches a method to treat implanted tumors in mice comprising the administration of an antisense oligonucleotide targeting DNA methyltransferase 1 and 5-aza-dC. Contrary to Applicants' assertions, it requires undue experimentation beyond that taught in the instant disclosure to enable the full scope of the claimed invention. The in vivo results obtained using one antisense oligonucleotide are not necessarily representative of in vivo efficacy using a different antisense oligonucleotide. Branch and Crooke, cited in the Office action mailed 5-8-02, elaborate on the inability to extrapolate in vitro data to in vivo efficacy, and teach that pharmacokinetics achieved with one antisense molecule are not predictive of others (see p. 10 of the Office action mailed 5-8-02). Crooke teaches that oligonucleotides may non-specifically interact with other biological molecules which are known to produce unpredictable effects, including non-antisense effects in a cell. The non-specific binding to proteins, lipids or carbohydrates may influence the ability of an effector molecule to reach its intended target and exert a desired effect. Branch also teaches how these molecules often act through entirely unexpected mechanisms, and that the successful delivery of antisense is unpredictable because cellular proteins can render target sites inaccessible in vivo (see pp. 10-11 of the Office action mailed 5-8-02). In addition, the treatment effects observed with one protein inhibitor are not representative of treatment effects that might

be provided using other protein inhibitors. The genus comprising *protein inhibitors of DNA methyl transferase 1* encompasses several types of protein inhibitors, which differ in structure and mechanism of action. A single inhibitor is not representative of this very broad genus. Synergistic treatment effects obtained using one protein inhibitor in combination with one antisense oligonucleotide are not predictive of treatment effects using other protein inhibitors in combination with an antisense oligonucleotide. Proper formulations required to obtain appropriate dosage, successful cellular targeting and treatment effects must be determined, all of which require undue experimentation beyond that taught in the instant disclosure. According to Branch, and as cited in the Office action mailed 5-8-02, "because it is very difficult to predict what portions of an RNA molecule will be accessible in vivo, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act..." (see p. 14 of the office action mailed 5-8-02, and see p. 49, col. 1, paragraphs 2-3 of Branch). Therefore, the claims are rejected for lacking enablement over the scope claimed, as well as for lacking adequate written description for the genus comprising protein inhibitors of DNA methyl transferase 1.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. 1.6(d)). The official fax telephone number for

the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JZ
10-13-04

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600